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NOVEL, MALONYL-DERIVED EDTA ANALOGUES

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ABSTRACT: Reaction of malonyl dichloride and benzylmalonyl dichloride with iminodiacetate esters has provided access to several, novel EDTA analogues.

As part of an ongoing programme aimed at developing biomimetic and metal-specific ligand systems, attention has been given to the synthesis of selected analogues of ethylenediaminetetraacetic acid (EDTA). The chelating properties of EDTA are, of course, well known and have been exploited in analytical and pharmaceutical [1] applications. Raymond and co-workers [2] have recently described the synthesis of diethylmalonyl-derived, vanadium-specific ligands, while De Santis *et al.*[3] have reported the development of redox-switchable analogues. In the malonyl-derived tetraacetate ligands discussed here, the active methylene centre of the malonyl moiety should permit linkage of the

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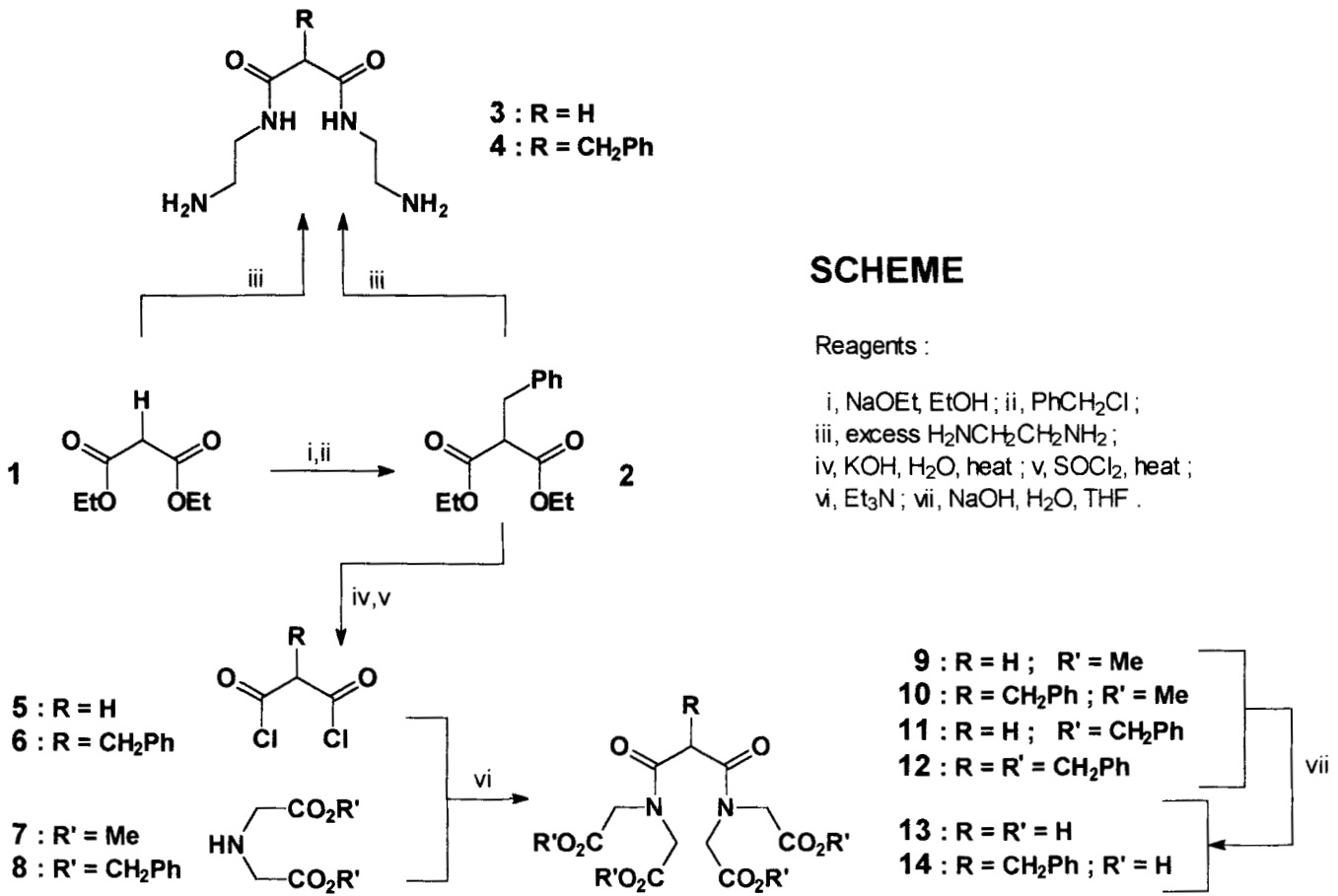
ligand system to lipophilic groups for solvent extraction or to solid supports for heterogeneous applications.

N,N'-Bis(2-aminoethyl)malondiamide **3**, which has been known for some time,[4] and its benzyl derivative **4**, reported for the first time in 1994,[3] have been prepared by treating the corresponding malonic esters with excess ethylenediamine, initially at 0°C and then at room temperature for a number of days. We have explored other procedures (*e.g.* heating the reactants at 160° for 8h, or treating malonyl dichloride with ethylenediamine in the presence of triethylamine) but, in all cases, purification of the products was problematic and these methods appear to offer no advantage over the reported procedures.[3,4]

The tetraacetate derivatives **9-14**, however, do not appear to have been reported previously and access to these interesting "EDTA analogues" is outlined in the Scheme, the benzylated derivatives being prepared as models of "linked" ligand systems. Using a variation of a reported procedure,[5] dimethyl iminodiacetate **7** was prepared from iminodiacetic acid, thionyl chloride and methanol, while the previously unknown dibenzyl analogue **8** was obtained in quantitative yield *via* the tosylate salt of iminodiacetic acid, following a protocol described by Williams and Rapoport.[6] Reaction of these iminodiacetate esters, **7** and **8**, with the malonyl dichlorides **5** and **6**, in the presence of triethylamine, afforded the four tetraacetate esters **9-12** in yields ranging from moderate to excellent.



SCHEME

Reagents :

i, NaOEt, EtOH ; ii, $PhCH_2Cl$;
iii, excess $H_2NCH_2CH_2NH_2$;
iv, KOH, H_2O, heat ; v, $SOCl_2$, heat ;
vi, Et_3N ; vii, NaOH, H_2O, THF .

While these esters could be conveniently purified by flash chromatography, their hydrolysis to the corresponding acids **13** and **14** presented some difficulties. Both acidic and basic hydrolysis of the *methyl* esters **9** and **10** was accompanied by partial hydrolysis of the amide functions, but it was found that basic hydrolysis of the *benzyl* esters **11** and **12**, followed by acidification, gave the required tetracarboxylic acids **13**[†] and **14**. However, work-up and attempted purification of these acids resulted in darkening and, under certain conditions, decomposition.

Analytical data for six of the seven new compounds[†] prepared in this study are summarised in the Table. The tetraesters **9-12** and the tetracarboxylic acids **13** and **14** each exhibit three carbonyl signals in their ^{13}C NMR spectra at 303 K. A variable temperature study of the methyl ester **9** in DMSO-d_6 revealed coalescence (at *ca.* 378 K) of the two, downfield carbonyl signals. The ^{13}C NMR signal doubling can thus be attributed to hindered rotation about the amide N-CO bonds, permitting assignment of the downfield carbonyl signals, in most cases, to the ester or acid moieties; in the case of the tetrabenzyl ester **12**, however, the shifts appear to be reversed. Doubling of other ^{13}C- and ^{1}H NMR signals is apparent (see Table) and is similarly attributed to rotational isomerism. The metal-chelating potential of these ligand systems will be examined in a future study.

[†] Although there is clear NMR evidence for the formation of the tetraacid **13**, this compound could not be obtained in sufficient purity to justify definitive characterisation.

TABLE Analytical data for new malonyl-derived ligand systems

Compd.	M.p. /°C	MS data [a]	^{1}H NMR data [b]/ppm	^{13}C NMR data [c]/ppm
8	—[d]	313,1296 (313,1314)	2.11(1H, br s), 3.51(4H, s), 5.16(4H, s), 7.34(10H, s).	50.1, 66.6, 128.3, 128.3, 128.5, 135.5, 171.5.
9	—[d]	390,1259 (390,1274)	3.58(2H,s), 3.68(6H,s)/3.72(6H,s),[e] 4.13(4H,s)/4.29(4H,s).	41.1, 48.3, 50.6, 52.1, 52.4, 166.9, 169.0/169.1.[e]
10	80-81°C	480,1726 (480,1744)	3.27(2H,d), 3.68(6H,s)/3.69(6H,s), 4.02-4.23(9H,m), 7.23(5H,m).	35.1, 48.8, 49.8, 50.9, 52.1, 52.4, 126.7, 128.6, 128.8, 138.4, 169.0, 169.1/169.2.
11	103-104°C	694,2515 (694,2526)	3.62(2H,s), 4.18(4H,s)/4.33(4H,s), 5.12(4H,s)/5.14(4H,s), 7.34(20H,m).	41.1, 48.5/50.8, 66.9/67.3, 128.2-128.6,[f] 135.0/135.3, 166.9, 168.4/168.5.
12	—[d]	784,2969 (784,2996)	3.25(2H,d), 4.0-4.25(9H,m), 5.10(8H,d), 7.10-7.40(25H,m).	35.1, 49.1/50.1, 50.8, 66.9/67.3, 126.6, 128.3-128.8,[f] 134.9/135.3, 138.4, 168.4/168.5, 169.2.
14	—[d]	—[g]	(DMSO-d_6) 3.06(2H,d), 3.85-4.30(9H,m), 7.20(5H,m).	(DMSO-d_6) 34.2, 47.3, 48.5/49.6, 126.1, 128.1, 128.5, 138.9, 168.8, 170.0/170.4.

[a] High resolution data (m/z) for the molecular ion followed, in parentheses, by the calculated value. [b] 400 MHz data in $CDCl_3$. [c] 100 MHz data in $CDCl_3$. [d] Oil. [e] The two chemical shift values quoted in this format, here and below, reflect signal splitting attributed to hindered rotation. [f] Overlapping aromatic signals; analysis complicated by rotational effects. [g] Peak for molecular ion not found.

EXPERIMENTAL

NMR spectra were obtained from $CDCl_3$ or DMSO-d_6 solutions on a Bruker AMX400 spectrometer and are referenced using the solvent signals. Low-resolution mass spectra were obtained by direct probe analysis on a Hewlett-Packard 5988A mass spectrometer and high-resolution data on a Kratos double-focusing magnetic sector instrument (Cape Technikon Mass Spectrometry Unit). The experimental procedures are illustrated by the following examples.

Dimethyl iminodiacetate **7**.[5] — Thionyl chloride (5.3 ml, 64 mmol) was added dropwise, with caution, to iminodiacetic acid (5.0 g, 38 mmol) in MeOH (30 ml). The resulting mixture was boiled under reflux, using a $CaCl_2$ drying tube, for 3h. The cooled reaction mixture was diluted with H_2O (20 ml), basified with 10% aq.NaOH and then extracted with EtOAc (2 x 30 ml). The extracts were combined and dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to afford dimethyl iminodiacetate **7** (4.6 g, 76%).

Dibenzyl iminodiacetate **8**. — A mixture of iminodiacetic acid (3.00 g, 22.5 mmol), *p*-toluenesulfonic acid (5.15 g, 27.1 mmol), benzyl alcohol (95 ml) and benzene (60 ml) was boiled under reflux, using a Dean-Stark trap, for 12h. After cooling, the precipitated solid was filtered off, washed with Et_2O and then suspended in $CHCl_3$ (120 ml). Addition of Et_3N (2.00 ml, 14.4 mmol) to the stirred suspension gave a clear solution which was then washed with dil. HCl.

Evaporation of the solvent *in vacuo* afforded an oil, which was dried *in vacuo* to give *dibenzyl iminodiacetate* **8** (7.23 g, 100%).

Tetrabenzyl malondiamide-N,N,N′,N′-*tetraacetate* **11**. — Malonyl dichloride (0.24 g, 1.7 mmol) was added in portions, using a syringe, to a stirred solution of dry Et_3N (0.51 ml, 3.7 mmol) and dibenzyl iminodiacetate **8** (1.05 g, 3.4 mmol) in dry THF (60 ml) under dry N_2. After stirring at room temperature for several hours, H_2O (20 ml) was added; the THF was then removed *in vacuo* and the residual aqueous phase extracted with EtOAc. The combined organic extracts were washed (satd. aq. NaCl) and dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residual yellow oil was chromatographed [flash chromatography on silica; elution with EtOAc-hexane (1:1)] to give colourless crystals of *tetrabenzyl malondiamide*-N,N,N′,N′-*tetraacetate* **11** (0.51 g, 43%).

2-Benzylmalondiamide-N,N,N′,N′-*tetraacetic acid* **14**. — Aq. NaOH(0.5*M*; 10 ml) was added to a solution of the tetrabenzyl ester **12** (0.20 g, 0.25 mmol) in THF (10 ml), and the resulting, heterogeneous mixture was stirred at room temperature for 1h. The aqueous phase was washed with benzene (2 x 20 ml) and acidified with 5*M*-HCl. Traces of organic solvent were removed *in vacuo* and the aqueous solution was passed through an Amberlite IR 120 ion-exchange column (acid-form). *In vacuo* evaporation of H_2O from the eluted solution at room temperature afforded a light-brown, solid residue, which darkened on

further drying *in vacuo* at 50°C. The product, which was very prone to decomposition, was shown by ^{1}H- and ^{13}C NMR spectroscopy to be the required *2-benzylmalondiamide*-N,N,N′,N′-*tetraacetic acid* **14** (0.09 g, 86%).

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